Clinical Research during an Emergency Response: Examples from 2009 H1N1

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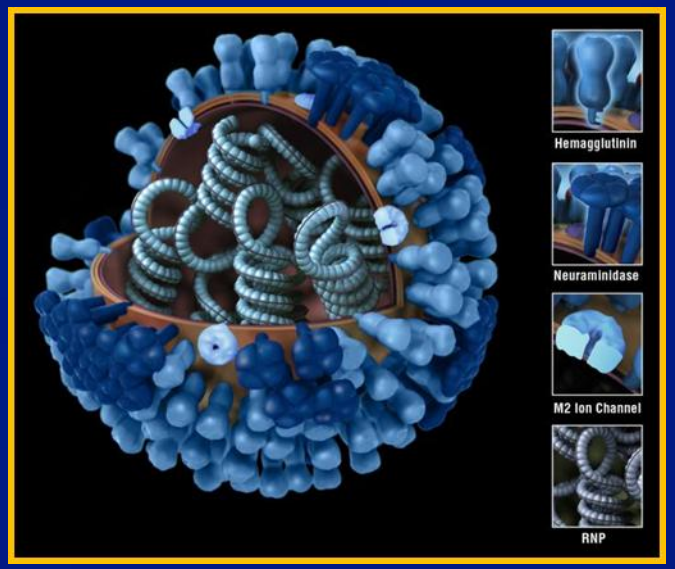


The findings and conclusions in this report are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

U.S Department of Health and Human Services
Centers for Disease Control and Prevention

Timeline of 2009 H1N1 Influenza Outbreak

- April 15, 17, 2009 – CDC identifies novel influenza A (H1N1) virus from 2 patients, US government notifies WHO
- April 26, 2009 – US declares public health emergency
- April 27, 29, June 11, 2009 – WHO raises global pandemic alert to phases 4/5/6
- August 10, 2010 – WHO declares end to 2009 H1N1 influenza pandemic

Impact of 2009 H1N1

- Estimated number of US cases: ~61 million
- Estimated number of US hospitalizations: ~274,000
- Estimated number of US deaths: ~12,470
  - 1,280 – 0-17 years
  - 9,570 – 18-64 years
  - 1,620 – 65 and older

http://www.cdc.gov/h1n1flu/estimates_2009_h1n1.htm

Two Examples

- Use of intravenous antiviral medications in critically ill patients
- Use of antiviral medications in pregnant women

Use of Intravenous (IV) Medications for Critically Ill Patients

- No FDA-approved IV influenza antiviral medications for treatment of severely ill, hospitalized patients
  - Is oral oseltamivir adequately absorbed in critically ill patients?
  - Inhaled zanamivir contraindicated for persons with underlying airway disease and mechanically ventilated patients

Peramivir Availability during 2009 H1N1

- Potential emergency use of investigational IV neuraminidase inhibitors (zanamivir, oseltamivir, and peramivir) assessed
- HHS acquired peramivir and FDA issued an Emergency Use Authorization (EUA) on October 23, 2009 (terminated on June 23, 2010)
- First time an investigational (unapproved) drug authorized for use under EUA

CDC's Peramivir EUA Program

- CDC developed and implemented an online system (Peramivir Electronic Request System) for clinicians to request peramivir for individual patients to ensure equitable, rapid access and web-based information for health care providers
- CDC conducted three post-release follow-up surveys

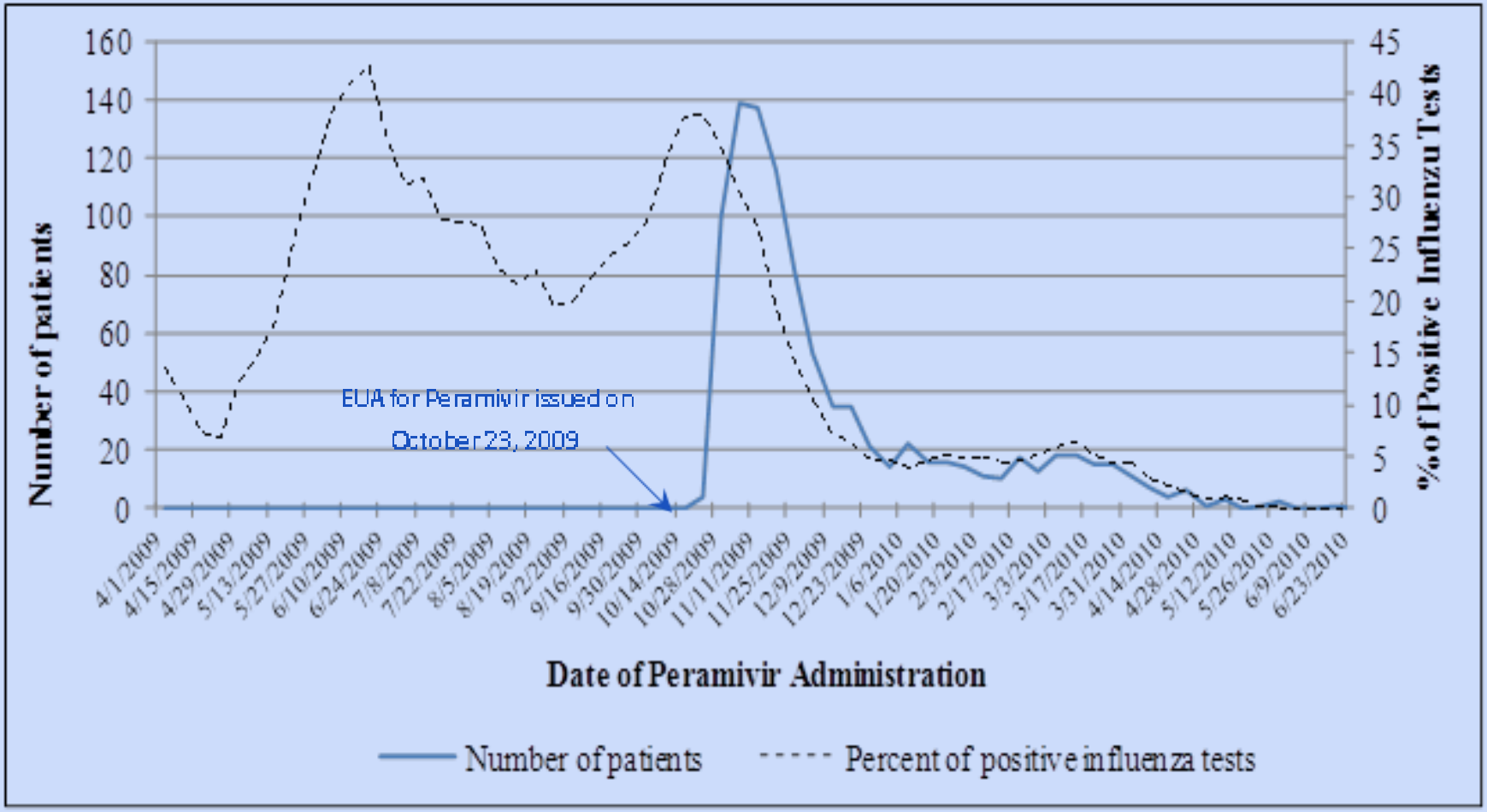
Yu Y et al., Clin Infect Dis 55:8-15, 2012

Peramivir Request/Distribution Data

- CDC received 1,371 requests for peramivir through the EUA program
- 2,129 five-day adult peramivir treatment course equivalents were delivered to 563 hospital pharmacies in the US and Puerto Rico within 24 hours of request (median delivery time: 12 hours)
  - Total quantity delivered is reflected as number of five-day adult treatment courses since the number of vials delivered varied based on adult or pediatric patient and 5- or 10- day courses
- 1,274 distinct peramivir recipients were identified

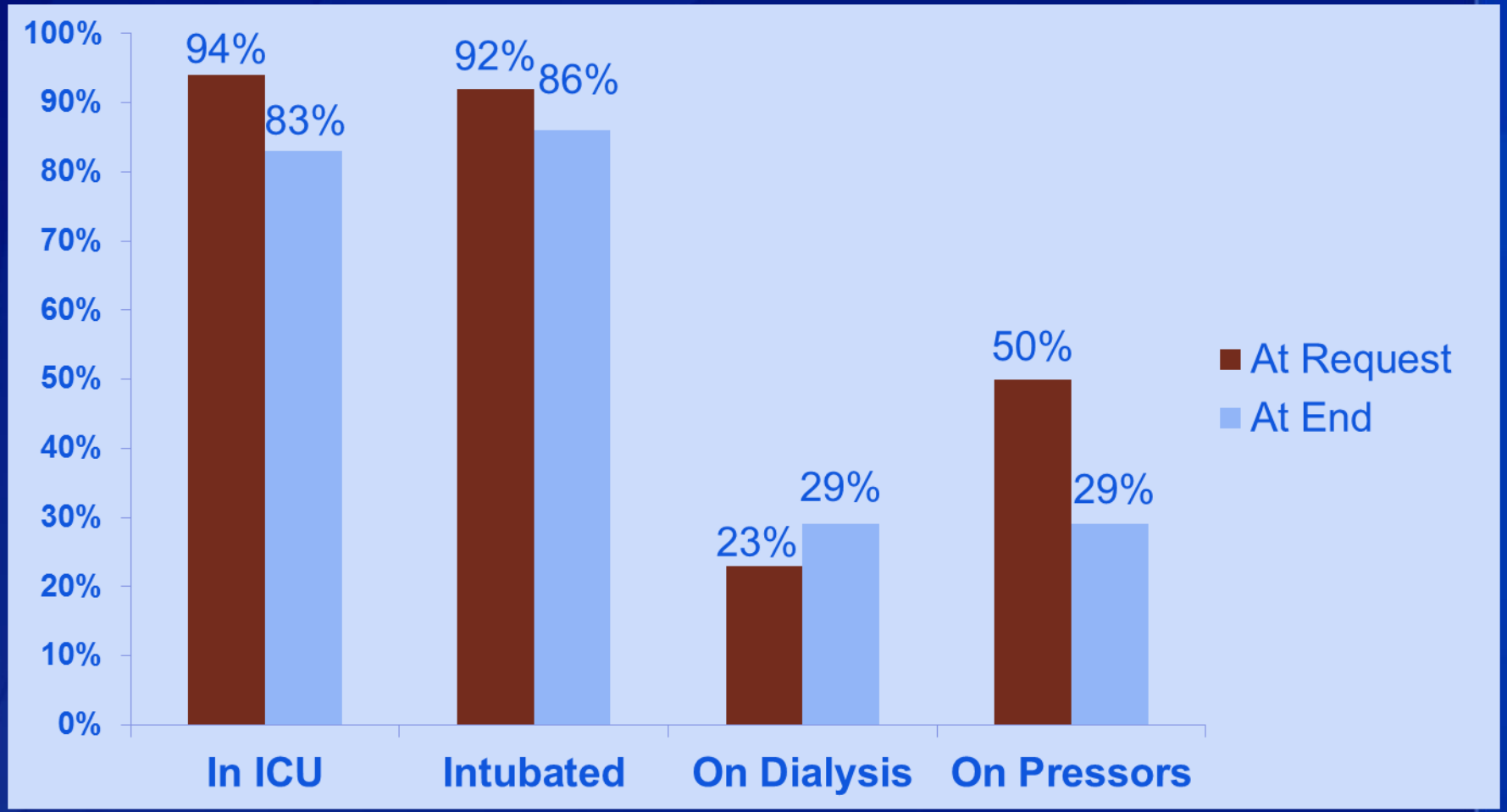
Yu Y et al., Clin Infect Dis 55:8-15, 2012

Frequency of Peramivir Administration during the EUA and Percent Positive Influenza Tests Reported to CDC during the 2009 H1N1 Pandemic



Yu Y et al., Clin Infect Dis 55:8-15, 2012

Patient Status Before and at End of Peramivir Treatment (N =127)



Yu Y et al., Clin Infect Dis 55:8-15, 2012

Adverse Events with Reporting Frequency ≥2% to FDA's Adverse Event Reporting System (N=344)

Adverse Event by Preferred Term (N)	%
Death (53)	15%
H1N1 influenza (26), respiratory failure (26)	8%
Acute respiratory distress syndrome (25), acute renal failure (25)	7%
Disease progression (21)	6%
Renal failure (17), hypotension (16)	5%
Cardiac arrest (15), no therapeutic response (14), pneumothorax (14), renal disorder (14), increased blood creatinine (13), pneumonia (13)	4%
Condition aggravated (12), hemodialysis (12), delirium (11), multiorgan failure (11), cardiorespiratory arrest (9), electromechanical dissociation (9), hypoxia (9)	3%
Agitation (8), increased alanine aminotransferase (8), increased aspartate aminotransferase (8), abnormal liver function test (8), renal impairment (8), rash (7), erythematous rash (7), brain death (6), continuous hemofiltration (6), general physical health deterioration (6), pyrexia (6)	2%

Sorbello A et al., Clin Infect Dis 55:1-7, 2012

Conclusions about Research on Peramivir

- Many peramivir recipients were critically ill and at risk for influenza-related complications
- Rash was the only treatment-emergent adverse event that was attributable to peramivir – difficult to distinguish between severe illness and adverse events
- Data collected were insufficient to assess whether peramivir affected outcome or caused adverse reactions other than rash

Use of Antiviral Medications in Pregnant Women

- Pregnant women are at increased risk for complications related to influenza
- Limited data are available on the use of antiviral medications for treatment of influenza during pregnancy

Pandemic Influenza and Pregnant Women: Summary of a Meeting of Experts

Pandemic Influenza: Special Considerations for Pregnant Women was a meeting convened by the Centers for

Sonja A. Rasmussen, MD, MS, Denise J. Jamieson, MD, MPH, Kitty MacFarlane, CNM, MPH, Janet D. Cragan, MD, MPH, Jennifer Williams, MSN, MPH, and Zsakeba Henderson, MD; for the Pandemic Influenza and Pregnancy Working Group

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MMWR

Dispatch

April 21, 2009 / 58 (Dispatch);1-3

Swine Influenza A (H1N1) Infection in Two Children --- Southern California, March--April 2009

2009-2010 Treatment Recommendations

- Treatment with oseltamivir is recommended for pregnant women and women up to 2 weeks postpartum with suspected or confirmed influenza, regardless of trimester of pregnancy
- Do not delay treatment because of a negative rapid influenza diagnostic test or inability to test or while awaiting test results

2009 H1N1 among Pregnant Women in the US, 2009

- ~ 5% of deaths in US from 2009 H1N1 influenza were among pregnant women (based on data from April-August 2009) -- pregnant women account for ~1% of the general population
- Early treatment was associated with fewer ICU admissions and fewer deaths

Siston et al., JAMA 303:1517-1525, 2010

Maternal Outcomes (ICU Admissions and Deaths) by Timing of Antiviral Treatment, US, April--August 21, 2009

Timing of treatment after symptom onset	Relative Risk (95% CI)	
	ICU Admissions	Deaths
>4 days vs. ≤2 days	6.0 (3.5-10.6)	53.5 (7.3-391.7)
3-4 days vs. ≤2 days	2.4 (1.2-4.8)	9.9 (1.1-87.2)

Siston et al., JAMA 303:1517-1525, 2010

Conclusions about Influenza Antiviral Medication Use in Pregnant Women

- Observational data suggest that pregnant women who received antiviral treatment were less likely to die and less likely to be admitted to the intensive care unit
- Knowledge about pharmacokinetics and safety of these medications during pregnancy remains severely limited

Overall Conclusions - 1

- Collecting data on safety and performance of medical countermeasures during a public health emergency response is challenging
  - Investigators are often actively working on response activities
  - Goals of providing rapid, equitable access to medical countermeasures and performing research may conflict
  - Research studies in the midst of a response might be perceived by public as using countermeasures that are not safe, decreasing the adherence to public health recommendations
  - Can adequate informed consent for research study be obtained in the event of a public health emergency response?

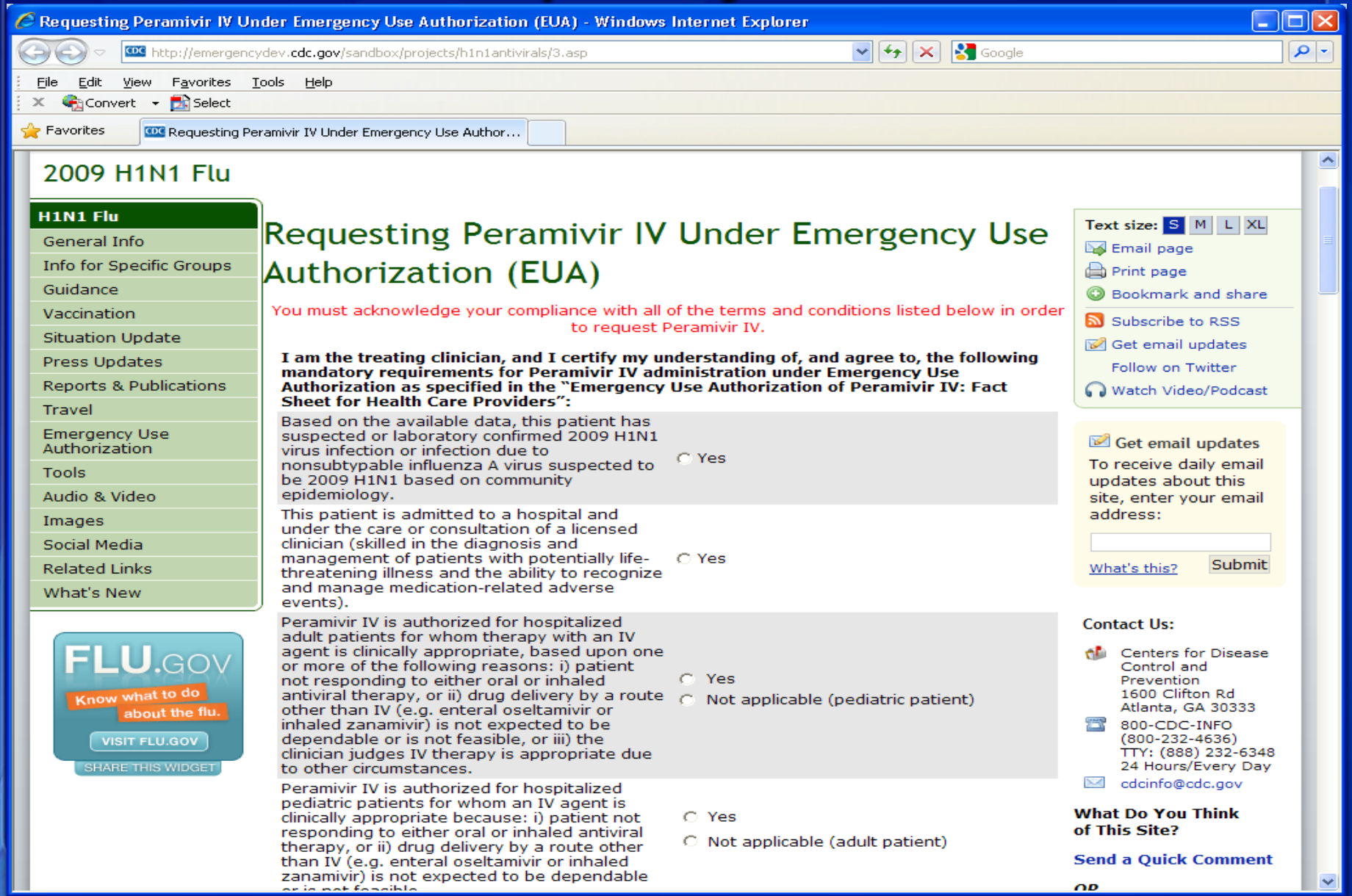
Overall Conclusions - 2

- Preparedness is key – need establishment (pre-event) of mechanisms (e.g., clinical networks) to conduct real-time or near real-time safety and clinical evaluation of investigational medical countermeasures
- A systematic mechanism for rapid review and analysis of reports/data collected during the event to inform and guide usage
- Studies would need rapid institutional review board review – could be facilitated by a central institutional review board

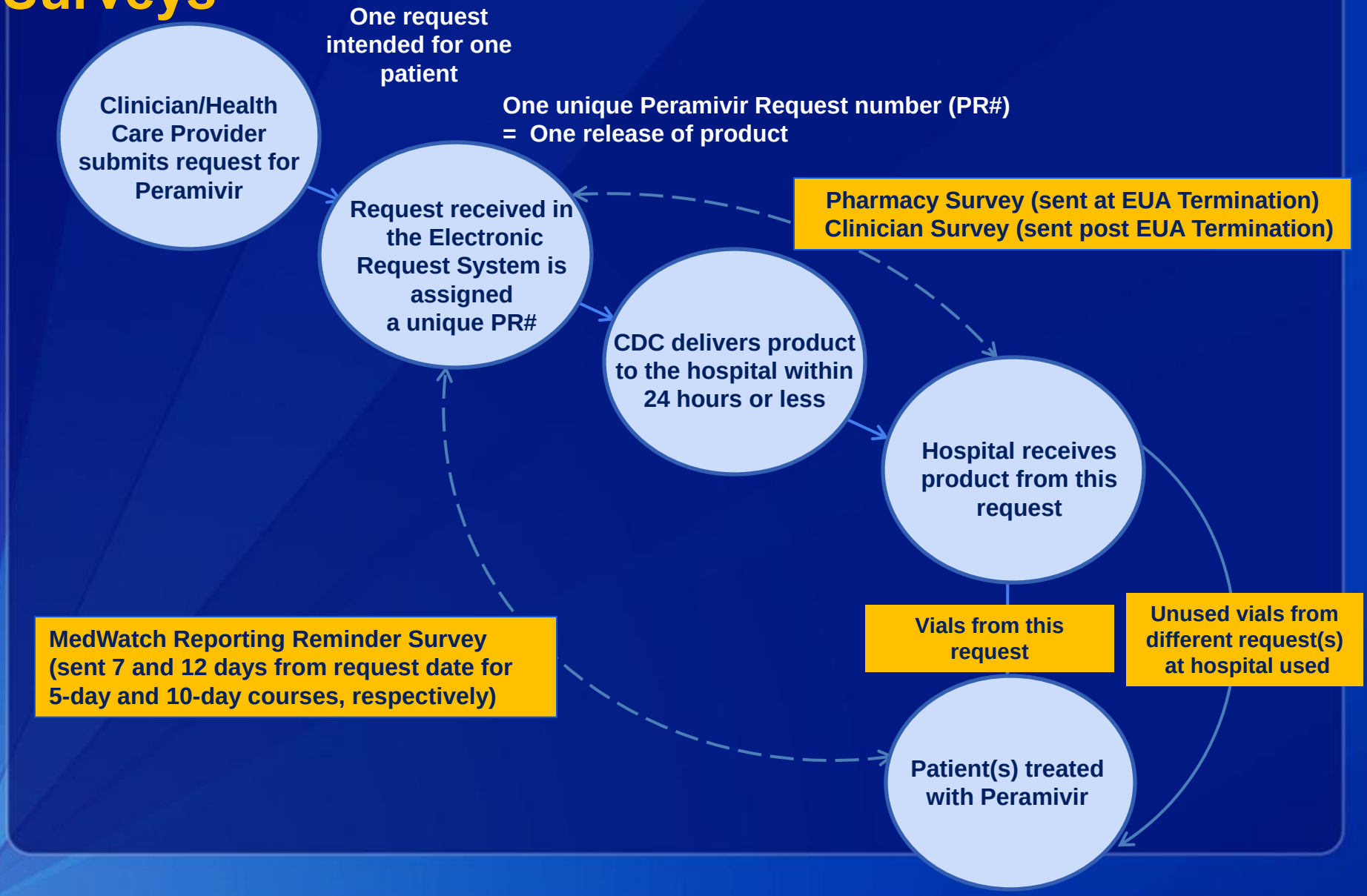
Acknowledgments

- Denise Jamieson
- Yon Yu

Snapshot of Peramivir Electronic Request System



Flow Chart of Peramivir Request Process and Surveys



Three Surveys

Survey Title	Survey Purpose	Duration of Survey	Participants	Response Rate
MedWatch Reporting Reminder Survey	To increase the clinicians' compliance with the MedWatch reporting requirement per FDA's EUA condition.	11/6/2009 through 6/23/2010	Requesting Clinicians	70% (963/1371)
Pharmacy Survey	To inform hospital pharmacies of EUA termination; To request product accountability information from hospital pharmacies	6/24/2010 through 8/31/2010	Hospital Pharmacies	79% (1080/1371)
Clinician Survey	To collect basic descriptive data on patients who were treated with peramivir	7/29/2010 through 8/17/2010	Requesting Clinicians	16% (160/1371)

Yu Y et al., Clin Infect Dis 55:8-15, 2012

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EDITORIAL COMMENTARY

What Did We Learn From the Emergency Use Authorization of Peramivir in 2009?

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(See the Major Articles by Yu et al, on pages XXX–X, and Sorbello et al, on pages YYY–Y.)

"A crisis is a terrible thing to waste." —Paul Rohmer

and only small clusters of secondary transmission were identified [6].

Two parenteral neuraminidase inhibi-

designed to collect epidemiologic and clinical data on peramivir recipients. Response rates for the MedWatch report-

Pavia A et al., Clin Infect Dis 55:16-18, 2012